Draft findings: Ethylene Oxide Carcinogenic Dose-Response Assessment; Development Support Document (DSD) proposed by Texas Commission on Environmental Quality (TCEQ) on June 28, 2019

Summary

TCEQ agreed with EPA that EtO is carcinogenic through a mutagenic mode of action but disagreed with the EPA's data modeling approach. *The TCEQ URF (URE) of 2.5 x 10^{-6} per ppb (1.4 x 10^{-6} per µg/m^3) was derived solely from analysis of lymphoid cancer mortality in men based on the NIOSH cohort.* TCEQ claimed the EPA URE of 9.1 x 10^{-3} per ppb (5.0 x 10^{-3} per µg/m^3; ADAF applied[1]) is too high because the most appropriate model was not used to fit the NIOSH data, and this caused overpredicted mortality. Therefore, TCEQ conducted its own toxicity assessment of the combined NIOSH and UCC cohorts (EPA did not use the UCC cohort data). TCEQ identified Valdez-Flores et al. (2010) as the key study, which analyzed grouped data from the NIOSH (Steenland et al., 2004) and UCC (Swaen et al., 2009) cohorts. TCEQ relied heavily on the Valdez-Flores analysis but derived its own point of departure using a 15-yr lag not adopted in the published study. Notably, TCEQ considered NIOSH breast cancer incidence data, but dismissed it because it was not "scientifically reasonable" for a URF to be below endogenous levels. The argument that the EPA's final URE is below endogenous levels was emphasized throughout the DSD to justify TCEQ's selection of a Cox proportional hazards model of the lymphoid cancer data.

Major claims presented by TCEQ

Note: all claims were previously addressed in EPA's final EtO assessment (2016) (Appendix K).

1) TCEQ: The UCC cohort (Valdez-Flores et al., 2010) should be analyzed in combination with the NIOSH cohort (Steenland et al., 2004) [TCEQ 3.2.1.2, p. 13]. *Note: After extensive analysis of both individual and combined datasets, TCEQ based the final URF only on the NIOSH cohort of men [TCEQ, p. 67].*
   EPA: EPA listed several solid reasons for excluding this study in its response to comments (e.g., women not represented). The SAB concurred with this decision [EPA (2016) Appendices K-6 and H-6 to H-8].
2) TCEQ: EPA URE corresponds to EtO exposure lower than endogenous levels estimated at 1.9 ppb by Kirman and Hays (2017). The small number of additional DNA adducts caused by EtO exposure would be overwhelmed by endogenous adduct levels with no statistical increase in cancer risk [TCEQ 3.4.1.2.1., p. 23].
   EPA: EPA did not accept this argument stating that ACC calculations (1 ppb) are unrealistic (EPA (2016) Appendix K-9). EPA cited Marsden et al. (2009) who found increases of DNA adducts from exogenous EtO exposure above those from endogenous EtO for very low exposures. [EPA (2016), Appendix C-30].
3) TCEQ: EPA's choice of a supralinear two-piece spline model was not the best fit at low exposures and in the absence of MOA justification the model should be no more than linear [TCEQ, p. 20]. TCEQ selected a Cox proportional hazards model which gave a sublinear fit of the lymphoid cancer data in the low dose range.
   EPA: The two-piece spline model was selected upon advice from SAB [EPA (2016), Appendix I-9] to best fit low exposure data. A linear Cox regression similar to TCEQ's selected model was also considered but was deemed not the best fit [EPA (2016), p. 4-10].

General Weaknesses in the proposed TCEQ DSD

1) The proposed TCEQ DSD has not been peer reviewed (but we understand that a letter peer-review is planned). TCEQ states that a statistician was contracted to confirm accuracy of the analyses and TCEQ guidelines indicate that the public comment period serves as "peer review" with the expectation that subject matter experts will choose to comment. Multiple typos of key details (e.g., EPA URE in executive summary) do not instill confidence that this document has received sufficient internal review.
2) New, unpublished follow-up data (through 2013) on the UCC cohort is used in the TCEQ analysis.

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[1] EPA URE (no ADAF applied) is 3.0 x 10^{-3} per µg/m^3, which is a more appropriate comparison to TCEQ's derived URF that did not include an ADAF (Note: TCEQ URF is three orders of magnitude lower than the EPA URE).

Questions about the TCEQ data analysis

1) Is the analysis comparing expected to predicted mortality from lymphoid cancer an appropriate and correct method for assessing model fit? (TCEQ DSD; Section A3.1, p. 99).
    a) Is TCEQ presenting enough information to replicate its findings?
        i) See TCEQ DSD Appendix 3 (starting on p. 98) and Table 32, p. 102

Questions for ORD about the EPA data analysis

1) Did EPA only use a subset of individual lymphohematopoietic cancer data as TCEQ claims? (TCEQ DSD, p. 101)
2) Should EPA have entered data into SAS differently to reflect that the knot was estimated outside of SAS, as TCEQ claims? (TCEQ DSD; Section A5.1.2, p. 125)
3) Does EPA have the original NIOSH data (both lymphoid and breast cancer)? Valdez-Flores et al. obtained the lymphohematopoietic cancer data through a FOIA request to NIOSH, but TCEQ claims the breast cancer data was not available to conduct a reanalysis.
    a) EPA noted the following in the final EtO assessment (2016): "With respect to the breast cancer incidence data, the EPA's Information Quality Act guidelines do not require that all underlying raw epidemiology data be publicly available; they allow for confidentiality constraints." [Appendix K-2]